UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D C 20231

09076404

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY DOCKET NO
09/076,404	05/12/98	ECHER	[illegible]0007

EXAMINER

HM12/0330

JOHN W CALDWELL
WOODCOCK WASHBURN KURTZ MACKIEWICZ
& NORRIS
ONE LIBERTY PLACE 46TH FLOOR
PHILADELPHIA PA 19103

ART UNIT	PAPER NUMBER
KAFAFI, S	15

DATE MAILED:
03/30/00

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 2/7/2000

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire Three month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-10 and 17-20 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 1-10 & 17-20 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☒ Claim(s) 1-10 & 17-20 are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892
☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 5, 2, 13
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

* U.S. GPO: 1996-404-498/40517

DETAILED ACTION

1. **The art unit designated for this application has changed. Applicant(s) are hereby informed that future correspondence should be directed to Art Unit 1631.**

2. This office action is in response to applicant's amendments and remarks dated 02/07/2000. The applicants canceled claims 11-16, and elected 1-10 and 17-20 claims as well as RNA as a species for examination. These claims will be examined without traverse.

3. The applicants are hereby notified that the computer readable sequence listing submitted earlier is unacceptable. The applicants need to submit a computer readable sequence listing in ASCII format.

4. The PCT search listed as reference AA on the PTO 1449 has been considered by this examiner. However, this reference has been lined-through because these reports are not published and 1999 appearing on the report is not a date of publication.

Specification

The last 4-lines of p. 2 and all of page 3 in the specification are duplicated in page 4 and the first 4-lines of page 5. Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-5, 6-10 and 17-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the application of the program DOCK for modeling the interactions of known molecules with a macromolecule's binding site, does not reasonably provide enablement for generally discovering the binding site(s) in macromolecules. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to discover the binding site(s) in macromolecules whose 3D-structure has not been determined by X-ray or NMR methods (**See the specification on p. 62, lines 6-13**). Even for macromolecules whose 3D-structures have been determined experimentally, DOCK cannot discover the ligands binding site(s), especially, if these sites are not on the exposed surface of the macromolecule. In fact, none of the commercially available software can discover any buried binding site(s) in macromolecules. The applicants do not decribe anywhere in the instant application how they were able to solve the latter problem. Thus, the invention is commensurate in scope with these claims.

In addition, on page 95 (2nd and 3rd paragraphs) the applicants describe the use of a standard Monte Carlo procedure for sampling the conformations of RNA! One skilled in the art would immediately realize that this is an impossible task for RNA molecules comprised of more than 2-3 dozens of base pairs. Therefore, for a typical RNA molecule comprised of few hundred base pairs, there are no available computational resources anywhere in the world that could sample its comformational space. Furthermore, the applicants then state on page 96 (first 2-lines) that structural refinement via molecular dynamics with explicit solvent and cations will be

performed. One skilled in the art also knows that molecular dynamic simulations are normally performed for few picoseconds on large molecular systems (few hundred atoms) using supercomputers. The applicants do not state for how long they intend to run these molecular dynamic simulations to refine the structures of the macromolecules of interest? How large are these molecules? And, how many solvent molecules they intend to incoporate in the computations? Accordingly, the applicants need to focus and narrow the scope of the claims as well as the specification because it would take undue experimentation by one skilled in the art using supercomputers that are not yet commercially available to perform the tasks stated *supra*.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

9. Claims 1-5, 6-10 and 17-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al "Structure-based discovery of ligands targeted to the RNA double helix." Biochemistry 36, 11402-11407, 1997 (PTO 1449).

10. Chen et al [p. 11402 (4th paragraph), and p. 11403 "DOCK calculations") discloses a method for identifying compounds which modulate the activity of a target (12-base pairs) RNA helix. First, Chen et al. identified the binding site and used the software DOCK to identify ligands that have potential to bind specifically to the major groove of the A-form duplex RNA. Each ligand was tested in thousands of orientations within the RNA binding site, and each orientation was evaluated by a scoring function. Only the best scoring orientation for each compound is stored, and compounds are ranked in order of their scores. The best candidates are then screened experimentally using a combination of NMR and spectrophotometric methods.

Chen et al differs from the instant application in using NMR and spectrophotometric methods instead of mass spectrometry for the manipulation of RNA-ligand complex. It must be noted that NMR, MS and X-ray crystallography are standard tools for obtaining structural informations pertaining to the structure and 3D conformations of marcromolecule-ligand complexes. It would have been obvious to one of ordinary skill in the art of drug design at the time the invention was made to use standard MS or NMR or X-ray crystallography for obtaining structural information on the macromolecule-ligand complexes of interest. One skilled in the art would be motivated to perform these structural experiments to check the validity of the

computational model, and refine it if necessary. Then, apply the computational model for the drug discovery process.

It is important to notice that it is standard in the art of drug discovery to experimentally screen the candidate compounds using the tools of organic synthesis, binding assays, X-ray crystallography, NMR, mass spectroscopy, GC-MS etc. Therefore, all of the elements in the instant application are anticipated by Chen et al.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Sherif A. Kafafi whose telephone number is (703) 305-0509. The examiner can be reached on Monday through Friday from 8:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Michael Woodward, can be reached on (703) 308-4028. The fax telephone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1234.

Sherif A. Kafafi, PhD

S. A. Kafafi

John D. Marschel

ARDIN H. MARSCHEL
PRIMARY EXAMINER

Art Unit 1631.

March 3, 2000